REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 1-4 are pending.

Rejections under 35 U.S.C. § 102

Claims 1, 3, and 4 stand rejected under 35 U.S.C. § 102 as purportedly anticipated by Kim (U.S. Patent No. 5,723,147). Kim purportedly discloses a process of preparation of liposomes in which the lipid in an organic solvent is added with an aqueous solution of an active agent which in turn is added with a second aqueous solution containing lysine. Kim purportedly further discloses various active agents including DNA and RNA. Applicants respectfully traverse.

"[A]nticipation requires the presence in a single prior art disclosure of all elements of a claimed invention as arranged in the claims." *Jamesbury Corp. v. Litton Industrial Products, Inc.* 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985). Kim does not describe or suggest all of the elements of the rejected claims, as discussed in greater detail below.

Independent claim 1 is directed to a method of encapsulating a bioactive into a liposome comprising dissolving at least one amphipathic lipid in one or more organic solvents, combining a first aqueous suspension comprising a bioactive agent with the lipid containing organic solution so as to form an emulsion comprising the bioactive agent and the lipid, adding a second aqueous suspension comprising a complexing agent to the emulsion,

incubating the emulsion to allow the complexing agent to contact the bioactive agent, forming a complex of the bioactive agent with the complexing agent within the lipid stabilized water droplets and removing the organic solvent from the suspension. The organic solvent is removed to form liposomes comprising the complexed bioactive agent and the lipid. Claim 1 also requires that the complex is no greater in diameter than the diameter of the droplet.

Kim fails to recite all of these elements. Kim discloses the formation of inclusion complexes of water-soluble compounds with cyclodextrins, and the encapsulation of the inclusion complex for controlled release. Specifically, Kim merely discloses the synthesis of multivesicular liposome-methotrexate-cyclodextrin formulation (MVL-CD-MTX), in Example 1 in columns 7-8. However, in describing this synthesis, Kim fails to recite all of the steps of present claim 1: dissolving at least one amphipathic lipid in one or more organic solvents, combining a first aqueous suspension comprising a bioactive agent with the lipid containing organic solution, adding a second aqueous suspension comprising a complexing agent to the emulsion, incubating the emulsion, forming a complex of the bioactive agent with the complexing agent within the lipid stabilized water droplets and removing the organic solvent from the suspension. Kim also fails to disclose that the complex be no greater in diameter than the diameter of the droplet.

Thus, as Kim fails to recite the elements of the present invention, Applicants request that this rejection be withdrawn.

Claim 1 stands rejected under 35 U.S.C. § 102(a) as purportedly anticipated by Kim

(*Cancer Research* 53: 1596-1598 (1993)). Kim purportedly discloses a process of preparation of liposomes in which the lipid in an organic solvent is added with an aqueous solution of an active agent which in turn is added with a second aqueous solution containing lysine. The organic solvent is then removed. Applicants traverse.

Kim fails to recite all of the elements of the present invention. Kim provides a discussion of the treatment of leptomeningeal leukemia or carcinomatosis using Depo/Ara-C (arabinofuranosylcytosine encapsulated in DepoFoam). However, in the discussion of the preparation of the Depo/Ara-C, Kim does not disclose the steps of the method of claim 1 of the present invention. Kim fails to disclose all of the steps of dissolving at least one amphipathic lipid in one or more organic solvents, combining a first aqueous suspension comprising a bioactive agent with the lipid containing organic solution, adding a second aqueous suspension comprising a complexing agent to the emulsion, incubating the emulsion, forming a complex of the bioactive agent with the complexing agent within the lipid stabilized water droplets, and removing the organic solvent from the suspension. Kim also fails to disclose that the complex be no greater in diameter than the diameter of the droplet.

Thus, as Kim fails to recite the elements of claim 1, Applicants request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claim 2 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Kim (U.S. Patent No. 5,723,147). As noted in the Office Action, Kim does not disclose the addition of the complexing agent to the lipid solution first followed by the addition of the

active agent solution. The Examiner argues that complexing occurs between the active agent and the complexing agent and states that the instant method steps are deemed to be manipulatable steps practiced by an artisan. Applicants traverse.

As set forth in M.P.E.P § 2142, in order to establish a prima facie case of obviousness, three criteria must be met, i.e., (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art references must teach or suggest all the claim limitations.

In the present case, 1) there is insufficient motivation to modify Kim in the manner proposed in the Official Action, there is no reasonable expectation of success of achieving the claimed method when modifying Kim.

Kim is directed to a multivesicular liposome system useful for providing prolonged and sustained *in vivo* exposure at a disease site of a therapeutic concentration of the biologically active substance. In contrast, the present invention provides methods which allow for the loading of bioactives into liposomes at high compound to lipid ratios. Prior to the present invention, high compound to lipid ratios were very difficult to achieve, especially with regard to large molecules such as nucleic acids. Efficient preparation and use of liposomal encapsulated bioactives required the use of high-concentration suspensions of the bioactive to minimize the percentage of empty liposomes resulting from the process and to maximize the bioactive to liposomal lipid ratios. Prior to the present invention, aggregation would often result from the high active:lipid ratios, creating complexes too large to

encapsulate or effectively administer to a patient in need. The present invention addresses this problem by providing methods of preparing liposomal encapsulations such that the bioactive is less permeable through the lipid bilayer and such that the size of the complex is limited and is therefore of an appropriate size for therapeutic applications.

Kim fails to address these issues, let alone provide a solution for them. Without even knowing the problems associated with complexed bioactives, let alone a solution, the skilled artisan would not have an expectation of success or have the motivation to modify Kim. In light of these comments, Applicants request that the rejection be withdrawn.

Claims 1-4 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Kim (U.S. Patent No. 5,759,573). The Office Action states that it would have been obvious to the skilled artisan to manipulate the basic process of preparation of liposomes, *i.e.*, adding the complexing agent and the active agent together in the same aqueous medium with the expectation of obtaining liposomes with similar complex. As noted in the Office Action, Kim does not specifically disclose a nucleic acid as an active agent.

As discussed above, Kim fails to recite the method steps of the present invention, or that the complex is no greater in diameter than the diameter of the water droplet. Further, Kim is directed to forming inclusion complexes of water-soluble compounds, such as methotrexate, with cyclodextrins and to encapsulating the inclusion complex into liposomes for controlled release. Specifically, the cyclodextrin forms an inclusion complex with the water soluble compound such that the apolar cavity of the cyclodextrin is occupied by or sequesters the compound sufficiently to slow the rate of release from the liposome

composition. The rim or the periphery of the inclusion complex is hydrophilic so that the inclusion complex forms a solution in aqueous media. This cyclodextrin-complexed water soluble substance is then encapsulated. Thus, Kim fails to provide the motivation to the skilled artisan to modify the methods of Kim to arrive at the claimed method, as Kim is directed to the use of cyclodextrin to create a controlled release composition.

In contrast, the methods of the present invention provide methods of preparing liposome encapsulated bioactives. The methods of the present invention allow for the loading of bioactives into liposomes at high compound to lipid rations. Prior to the present invention, aggregation would often result from the high active:lipid ratios, creating complexes too large to encapsulate or effectively administer to a patient in need. The present invention addresses this problem by providing methods of preparing liposomal encapsulations such that the bioactive is less permeable through the lipid bilayer and such that the size of the complex is limited and is therefore of an appropriate size for therapeutic applications.

Kim fails to address these issues, let alone provide a solution for them. Without even knowing the problems associated with complexed bioactives, let alone a solution, the skilled artisan would not have an expectation of success.

In light of the above remarks, Applicants request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

In the event any further fees are due to maintain pendency of this application, the Examiner is authorized to charge such fees to Deposit Account No. 02-4800.

Respectfully submitted,

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